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An Enantiospecific Synthesis of 4-Methylcamphor

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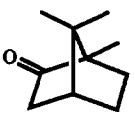
Abstract : Treatment of (-)-2-methylenebornane (**7**), derived from (+)-camphor (**1**), with 45% HBr /HOAc results in Wagner-Meerwein rearrangement and formation of 4-methylisobornyl bromide (**17**) in 80-90% yield. The enantiopurity of (**17**) was determined by conversion to (+)-4-methylisoborneol (**5**) and (-)-4-methylcamphor (**3**).

Investigations by a number of research groups[1] have shown that (+)-camphor (**1**) or (-)-camphor (**ent-1**) and appropriate derivatives can be used as enantiopure intermediates in steroid and terpenoid synthesis. With respect to steroid synthesis we have illustrated[2] the versatility of (+)-9,10-dibromocamphor (**2**)[3] and (**ent-2**) as enantiopure intermediates in the synthesis of the C,D ring system and side-chain unit in these compounds.



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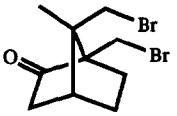

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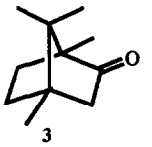

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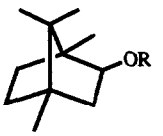


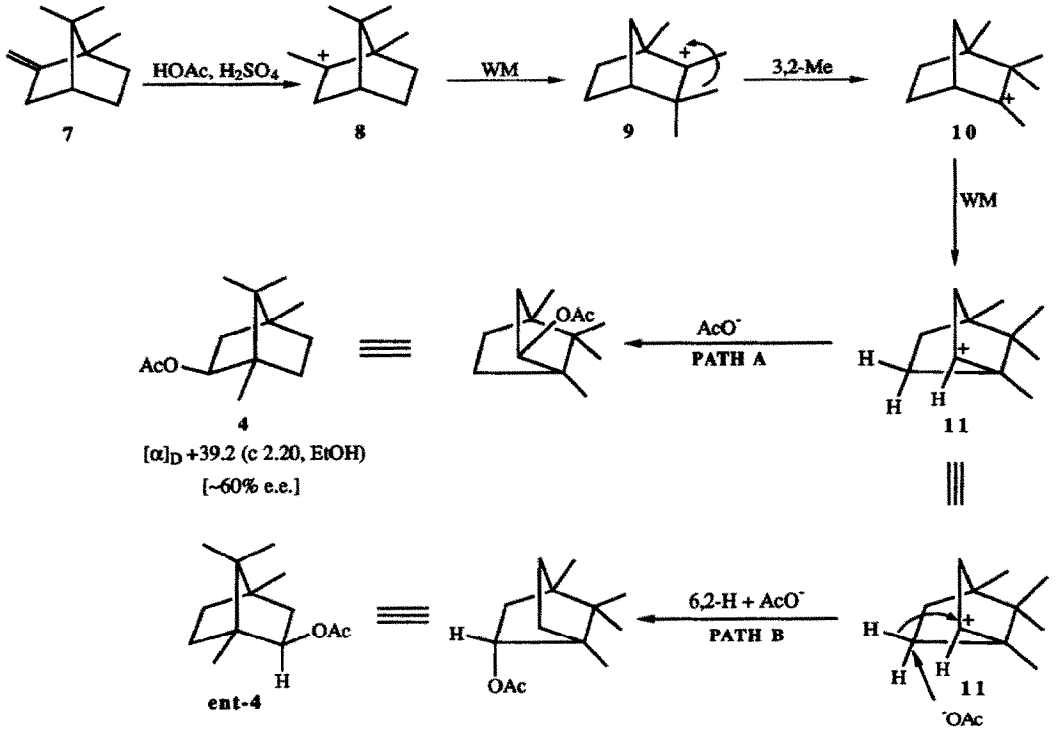
4 [R = Ac]
5 [R = H]
6 [R = NO_2]

The extension of this chemistry to (-)-4-methylcamphor (**3**) and its enantiomer (**ent-3**) should be possible and could provide enantiopure intermediates for the synthesis of lanostane-type and euphane-type triterpenoids. However recent studies[4] have shown that none of the published synthetic routes[4-9] to 4-methylcamphor via 4-methylisobornyl acetate (**4**)[4-6], 4-methylisoborneol (**5**)[7,8] or 4-methylisobornyl nitrate (**6**)[9] provides material that is enantiopure.

A general mechanistic explanation for these experimental results is based on the assumption that the published synthetic routes to intermediates (**4**) - (**6**) involve a carbocation intermediate (**10**) [Scheme 1] that can rearrange in two alternative ways. In one pathway [**A**, Scheme 1] Wagner-Meerwein rearrangement of (**10**) followed by addition of acetate, nitrate, or water to carbocation (**11**) provides (+)-4-methylisobornyl acetate (**4**) or the corresponding alcohol (**5**) or nitrate (**6**). In the alternative pathway [**B**, Scheme 1] carbocation (**11**) undergoes 6,2-hydride shift followed by addition of acetate, water or nitrate to provide (-)-4-methylisobornyl acetate (**ent-4**) or the corresponding alcohol (**ent-5**) or nitrate (**ent-6**). Thus it seemed obvious that the synthesis of enantiopure 4-methylcamphor from 2-methylenebornane (**7**) could only be accomplished by suppression of the 6,2-hydride shift [path B, Scheme 1] that leads to the enantiomeric series. However, several recent attempts[4b] to accomplish this objective by treating C(5)-substituted 2-methylenebornane derivatives with $HOAc/H_2SO_4$ were unsuccessful.

As a result of this failure we re-examined literature reports that describe significant investigations on the rearrangement of bicyclo[2.2.1]heptyl carbocations[10,11]. The classical studies by Roberts[12], Winstein[13] and their

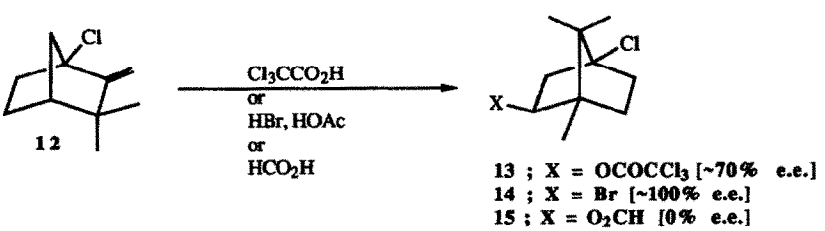
respective co-workers have shown that the relative tendency[14] of norbornyl carbocations to undergo Wagner-Meerwein rearrangement and 6,2-hydride shift can be affected by reaction conditions. From the results of numerous investigations[4-9,15-17] it is also evident that bicyclo[2.2.1]heptyl carbocations [cf. **11**, Scheme 1],



WM = Wagner-Meerwein rearrangement ; 3,2-Me = exo-3,2-methyl shift ; 6,2-H = endo-6,2-hydride

Scheme 1

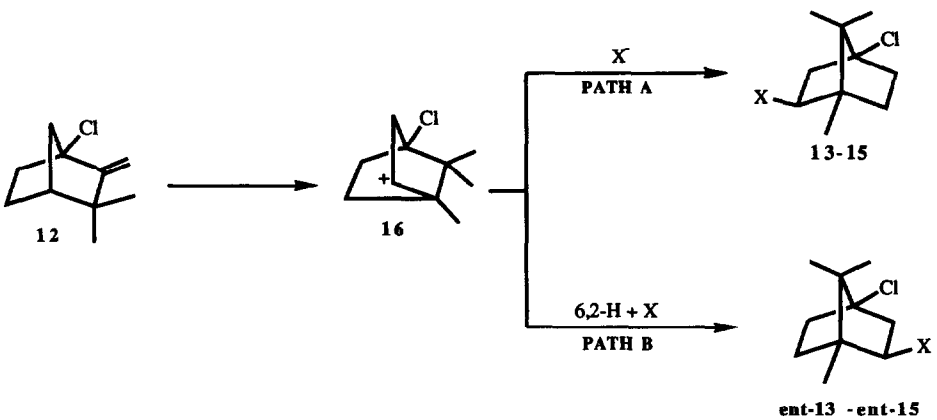
produced by Wagner-Meerwein rearrangement, can either react with nucleophile directly [cf. path A, Scheme 1] or undergo 6,2-hydride shift followed by reaction with nucleophile [cf. path B, Scheme 1]. In structurally appropriate cases the relative rate of these reaction pathways is reflected in the enantiomeric purity of the product and there is a reasonable amount of experimental evidence[12,13,15-17] to support the view that the proportion of enantiomers [i.e. relative rate of reaction of carbocation with nucleophile versus rate of 6,2-hydride shift] can be adjusted by a suitable choice of reaction conditions. Specifically relevant to the enantiospecific synthesis of 4-



13 ; X = OCOCCl3 [~70% e.e.]
14 ; X = Br [~100% e.e.]
15 ; X = O2CH [0% e.e.]

methylcamphor (**3**) are the reported transformations of 1-chlorocamphene (**12**)[15-17] to products, (**13**)-(**15**), whose enantiomeric purity was markedly dependent on reaction conditions.

An explanation for the variation in enantiomeric purity of the products derived from 1-chlorocamphene (**12**) has not previously been proposed. However, it is reasonable to assume that these rearrangements involve an intermediate carbocation [**16** ; Scheme 2] that can either react with nucleophile directly [path A] or undergo 6,2-hydride shift before reacting with nucleophile [path B, Scheme 2]. In addition, the relative rates of these two processes is reflected in the enantiomeric purity of the products. Of particular significance, however, is the observation[16] that treatment of 1-chlorocamphene (**12**) with 45% HBr/HOAc provides enantiopure 4-chloro-isobornyl bromide (**14**). Thus it seems that in this reaction the nucleophilicity of bromide ion results in exclusive capture of the intermediate carbocation (**16**) before it can undergo 6,2-hydride shift.

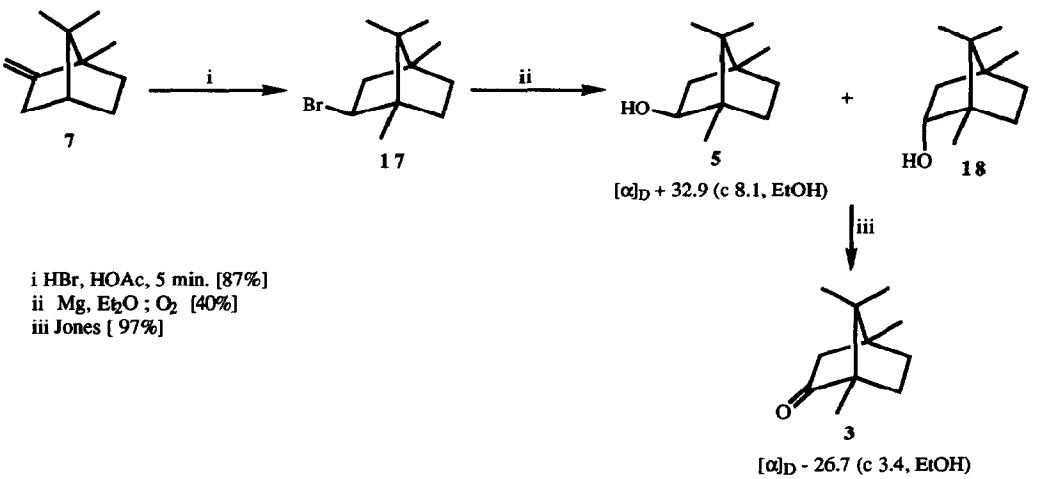


Scheme 2

The similarity between intermediates (**11**) [Scheme 1] and (**16**) [Scheme 2] led us to examine the rearrangement of (-)-2-methylenebornane (**7**)[18] in the presence of 45% HBr/HOAc and, as a result, we have recently established (Scheme 3) that treatment of (**7**) with this reagent for 5 minutes at room temperature provides 4-methylisobornyl bromide (**17**) in 80-90% yield. The enantiomeric purity of this compound was determined by converting the Grignard derivative of (**17**) to a mixture of (+)-4-methylisoborneol (**5**) and 4-methylborneol (**18**). Separation of (**5**) from its epimer (**18**) was accomplished by column chromatography and spectroscopic [ir, nmr, ms] and glc characteristics of (**5**) were identical to those previously recorded[4a] for enantioenriched 4-methylisoborneol (**5** + **ent-5**). However, the specific rotation ($[\alpha]_D$ +33, c 8.1, EtOH) of this sample of (**5**) was significantly higher than that ($[\alpha]_D$ +20-25) previously reported[4a,5,9] for this compound. The enantiomeric purity of (**5**) was first estimated from comparative chromatograms obtained for enantioenriched 4-methylisoborneol (**5** , ~60% e.e.) [sample A][4a] and "enantiopure" (**5**) [sample B] using a Chirasil-val III capillary column [Alltech, 25 m × 0.25 mm i.d.] and these clearly showed that, within the detection limits of this glc system, sample B of 4-methylisoborneol produced by our new procedure (Scheme 3) was enantiopure[19]. In addition samples A and B were esterified[21] with α-methoxy-α-trifluoro-methylphenylacetic acid[22,23] [Mosher acid, MTPA] and, after purification by column chromatography, the ^{1}H-nmr spectra [400 MHz] of the derived esters were recorded. In the ^{1}H-nmr spectrum of the Mosher ester derived from sample A of 4-methylisoborneol two signals of unequal intensity [~1:2.5] at 4.78 δ (doublet of doublets, J = 3 Hz, 8 Hz ; C(3)-endo H ; minor diastereomer) and 4.91δ (doublet of doublets, J = 3 Hz, 8 Hz ; C(3)-endo H ; major diastereomer) were clearly evident. Extra signals in the methyl region of the spectrum [cf. experimental section] were also consistent with the presence of diastereomeric Mosher esters. In contrast, the ^{1}H-nmr of the Mosher ester derived from sample

B [~100% e.e.] showed only a doublet of doublets centred at 4.89δ and no evidence for the signal at 4.78δ. In addition four singlet absorptions due to the four methyl groups in this ester were clearly evident.

Further confirmation of the enantiopurity of sample B of 4-methylisoborneol (**5**) was obtained by conversion to (-)-4-methylcamphor (**3**) ($[\alpha]_D$ -26.7, c 3.4, EtOH)(Scheme 3) and comparing the ^{1}H-nmr spectrum of (**3**) in the presence of a chiral shift reagent [0.5-0.7 molar ratio of Eu(hfc)$_3$] with that obtained[4a] for the enantioenriched material (**3**, ~60% e.e.; $[\alpha]_D$ -16.0, c 2.04, EtOH) derived from sample A. In the latter case, as indicated in our previous report[4a], the C(10) methyl group was clearly seen as two signals of unequal intensity (3-4:1) while the nmr spectrum of the sample of (**3**) produced by our new procedure (Scheme 3) was devoid of "extra" peaks due to the presence of (**ent-3**).



Scheme 3

The availability of enantiopure 4-methylcamphor (**3**) has provided us with the opportunity to assess the potential of this compound and its enantiomer as synthetic precursors of the C,D ring system of lanostane and euphane triterpenoids and investigations in this area are underway in our laboratory. In addition, attempts will be made to increase the yield [40%] in the conversion of 4-methylisobornyl bromide (**17**) to the mixture of (+)-4-methylisoborneol (**5**) and 4-methylborneol (**18**).

Acknowledgement

We are grateful to N.S.E.R.C., Ottawa, Canada for financial support of this project.

Experimental

All reagents were commercial grade and were used as received unless otherwise indicated. Reactions involving air- or moisture-sensitive reagents were carried out in flame- or oven-dried glassware under an argon atmosphere. Dry tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone.

Thin layer chromatography was performed on Merck 5735 Precoated Silica Gel 60, PF_{254} on plastic

sheets, and visualisation involved the use of iodine vapour or ammonium molybdate/H_2SO_4 spray. Gas liquid chromatography (glc) was performed on a Hewlett-Packard HP5830A instrument [OV-101 column ; 0.2 mm x 11 m] or a Hewlett-Packard HP 5880A [Chirasil-val III column ; 0.25 mm × 25 m] with helium as carrier gas. Column chromatography was performed on Merck Silica Gel 60 [70-230 or 230-400 mesh] . Radial chromatography was performed on a Harrison Research Chromatotron® 7924T using plates of Merck Silica Gel 60, PF_{254}, containing gypsum, of 1, 2, or 4 mm thickness and 4.0 - 11.25 cm radius.

Infrared (IR) spectra were recorded on a Perkin Elmer 710B scanning spectrophotometer or a Bomem Michelson 100 Fourier Transform Infrared spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker WH-400 or Bruker AMX-500 spectrometer with signal positions referenced to tetramethylsilane (TMS). Low resolution mass spectra were recorded on a Kratos MS-80 spectrometer and high resolution mass spectra were recorded on a Kratos MS-50 spectrometer.

Specific rotations were recorded at 589 nm [sodium D line] on a Jasco J-710 polarimeter using a 1 dm cell. Melting points were measured on a Reichert heating stage, and are uncorrected. Elemental analyses were performed by Mr. P. Borda, Microanalytical Laboratory, Department of Chemistry, UBC.

(-)-2-Methylenebornane (7)[18]

To methyltriphenylphosphonium bromide (79.7 g, 0.223 mol) that had been dried under vacuum (~0.1 torr) for 12 h was added dry THF (~200 mL). The resulting slurry was kept under argon and n-BuLi (~139 mL, 1.6 M/hexane, 0.223 mol) was added dropwise until a red solution was obtained. After heating the solution at 50°C for 2 h, a solution of (+)-camphor (**1**, 21.2 g, 0.139 mol) in dry THF (80 mL) was slowly added. A white precipitate was obtained and the yellow-orange reaction mixture was refluxed for 24 h. After cooling, approximately half of the solvent was removed, water was added and the mixture extracted with pentane (3x). The combined extracts were washed with water (3x), dried over $MgSO_4$, and the solvent removed to give a crude product that was purified by column chromatography using pet. ether as eluant to provide (-)-2-methylenebornane (**7**) as a white solid (18.2 g, 87% yield), m.p. 70-71° (sealed tube) ; lit.[18b] m.p.68-69°.

$[\alpha]_D$ -52.88 (c 2.67, benzene) ; lit.[18b] $[\alpha]_D$ -48.5 (c 2.12, benzene)
$C_{11}H_{18}$, HRMS , calc. mass : 150.1409 ; found : 150.1400
$C_{11}H_{18}$, calc.% : C 87.93 , H 12.07 , found : C 87.87 , H 11.99
^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm : 0.76 (3H, s, CH_3); 0.89 (3H, s, CH_3); 0.92 (3H, s, CH_3); 1.15-1.30 (2H, m, C(5) and C(6) endo H's); 1.64 (1H, ddd, J=12, 12, 4 Hz, C(6) exo H); 1.73 (1H, dd, J=8, 4 Hz, C(4)H); 1.78 (1H, m, C(5) exo H); 1.91(1H, dt, J=16, 1.5 Hz, C(3) endo H); 2.38 (1H, br d, J=16 Hz, C(3) exo H); 4.63 (1H, s, vinyl H); 4.69 (1H, s, vinyl H).
IR ($CHCl_3$): ν_{max} 1655 , 878 cm^{-1}
MS m/e(%) : 150 (M^+, 22); 135 (38); 107 (100); 93 (66); 79 (72); 67 (19).

4-Methylisobornyl bromide (17)

To a solution of (-)-2-methylenebornane (**7** ; 1.91 g, 12.7 mmol) in HOAc (8.0 mL) was added 45% HBr/HOAc solution (8.0 mL). After 5 minutes the mixture was cautiously poured into water, extracted with ether (3x) and the combined extracts washed with water (3x), $NaHCO_3$ solution (3x) and water (3x). Drying over $MgSO_4$ and removal of the solvent gave a yellow solid that was purified by flash column chromatography using pet.ether : ether [15:1] as eluant to provide 4-methylisobornyl bromide (**17**) as a white solid (2.55 g, 87% yield). This compound discoloured upon storage and was therefore always freshly prepared and used immediately in the next reaction.

$C_{11}H_{19}{}^{79}Br$, HRMS ; calc. mass : 230.0670 , found : 230.0663
$C_{11}H_{19}{}^{81}Br$, HRMS ; calc. mass : 232.0650 , found : 232.0645
^{1}H-NMR (400 MHz, $CDCl_3$) : δ 0.72 (3H, s, CH_3; 0.91 (3H, s, CH_3); 1.00 (3H, s, CH_3); 1.07 (3H, s, CH_3); 1.15-1.22 (2H, m); 1.42-1.49 (1H, m); 1.70-1.76 (1H, m); 2.10-2.15 (2H, m, C(3) exo and endo H's); 4.15 (1H, dd, J=8, 5 Hz, C(2) endo H).
MS m/e(%) : 232, 230 (M^+, 0.4, 0.5); 217, 215 (4.2, 3.7); 151 (89); 150 (71); 135 (82); 121 (75); 107 (100); 95 (91); 81 (86).

(+)-4-Methylisoborneol (5) and 4-Methylborneol (18)

To freshly ground, flame-dried Mg (0.60 g, 0.025 mol) under argon was added a crystal of iodine and dry THF (6.0 mL). After the dropwise addition of dibromoethane (0.51 mL, 6.0 mmol) to initiate Grignard formation, a solution of 4-methylisobornyl bromide (**17**) (2.76 g, 11.9 mmol) in dry THF (5.0 mL) was added at a rate to maintain vigorous reaction. The mixture was stirred for ~30 min and dry THF (19.0 mL) was added. [**Caution** : In the next step of the reaction, potentially explosive peroxides are formed and therefore the use of a blast shield is recommended]. Oxygen (dried by passage through 4Å molecular sieves and Drierite) was bubbled through the reaction mixture for 1.5 h and the mixture was kept under argon overnight. Hydrochloric acid (1M) was cautiously added and the mixture was extracted with ether (3x). The combined extracts were washed with water (2x), $NaHCO_3$(aq) solution (2x), water (2x), and dried over $MgSO_4$. Removal of the solvent provided a pale yellow liquid that was purified by column chromatography [eluant pet.ether : ether , 9:1] to give (+)-4-methylisoborneol (**5**) (0.26 g, 13% yield) as a white solid, ($[\alpha]_D$ +32.9 (c 8.1, 95% EtOH) ; lit.[4a] +19.5 (c 10.0, EtOH) ; lit.[9] + 25.2 (c 10.0, EtOH) ; lit.[5] +22.69 (EtOH)) and a mixture (6:1) of (+)-4-methylisoborneol (**5**) and 4-methylborneol (**18**) (0.53 g, 27% yield).

$C_{11}H_{20}O$, HRMS, calc. mass : 168.1514 , found, 168.1511
$C_{11}H_{20}O$, calc. % : C 78.51, H 11.98 , found : C 78.53, H 12.12
^{1}H-NMR (400 MHz, $CDCl_3$) **5** : δ 0.68 (3H, s, CH_3); 0.87 (3H, s, CH); 0.90 (3H, s, CH_3); 0.94 (3H, s, CH_3); 0.95-1.11 (2H, m, C(5) and C(6) endo H's); 1.35-1.46 (2H, m, C(6) and C(3) endo H's); 1.51 (1H, ddd, J=8, 8, 4 Hz, C(5) exo H); 1.74 (1H, dd, J = 14 Hz, 8 Hz ; C(3) exo H); 3.61 (1H, dd, J = 8 Hz, 4 Hz; C(2) endo-H).
^{1}H-NMR (400 MHz, $CDCl_3$) **18** : δ 0.71 (3H, s, CH_3); 0.73 (3H, s, CH_3); 0.83 (3H, s, CH_3); 0.86 (3H, s, CH_3); 1.02 (1H, dd, J=13, 4 Hz); 1.18-1.30 (2H, m); 1.44-1.51 (1H, m); 1.82-1.90 (1H, m); 1.93-2.03 (1H, m); 3.94 (1H, br d, J=11 Hz, C(2) exo-H).
IR ($CHCl_3$) : ν_{max} 3615 cm^{-1}
MS m/e(%) : 168 (M^+, 2.6); 124 (28); 109 (100); 84 (29); 55 (28); 41 (35).

Estimation of Enantiomeric Purity of (+)-4-Methylisoborneol (5)

(1) Using a Chiral glc Column

Sample A of (+)-4-methylisoborneol (**5**) (~60% e.e.; $[\alpha]_D$ +20) and Sample B of (+)-4-methylisoborneol ($[\alpha]_D$ +33) were separately analysed using a HP 5880A chromatograph with a Chirasil-val III capillary glc column (Alltech, 25 m × 0.25 mm i.d.) (helium flow rate, 1.46 mL/min; oven temp. 60°).
Sample A rt 29.90 min and rt 30.70 min [relative areas ~ 4:1]
Sample B rt 29.93 min
(2) Mosher ester analysis

Mosher ester derived from sample A :

^{1}H-NMR [500 MHz, $CDCl_3$] : δ 0.60 (0.3 CH_3, s), 0.66 (1.0 CH_3, s), 0.69 (0.7 CH_3, s), 0.78 (0.7 CH_3, s), 0.86 (0.3 CH_3, s), 0.88 (0.3 CH_3, s), 0.90 (0.7 CH_3, s), 4.78 (0.3 H, dd, J = 3.5 Hz, 8 Hz ; C(2) endo H) ; 4.91 (0.7 H, dd, J = 3.5 Hz, 8 Hz ; C(2) endo H)

Mosher ester derived from sample B :

^{1}H-NMR [400 MHz, $CDCl_3$] : δ 0.64 (3H, s), 0.67 (3H, s), 0.76 (3H, s), 0.88 (3H, s), 4.89 (1 H, dd, J = 3.5 Hz, 8 Hz ; C(2) endo H) ,

(-)-4-Methylcamphor (3)

A solution of CrO_3 (0.089 g, 0.89 mmol) in water (1.2 mL) and H_2SO_4(conc) (0.3 mL) was added dropwise to a solution of (+)-4-methylisoborneol (**5**) and 4-methylborneol (**18**) (0.075 g, 0.45 mmol) in acetone (5.0 mL) at 0°C. After the addition of the orange reagent was complete, the reaction mixture turned green and was stirred at room temperature for 1 h. Water was added and the mixture was extracted with ether (3x). The combined extracts were washed successively with water (3x), $NaHCO_3$(aq) solution (2x), water (2x), dried over $MgSO_4$ and the solvent removed to give a white solid. Purification by column chromatography using pet.ether : ether [15:1] as eluant gave (-)-4-methylcamphor (**3**) as a white solid (0.072 g, 97% yield).

$[\alpha]_D$ -26.7 (c 3.4, 95% EtOH) ; lit.[4a] $[\alpha]_D$ -16.0 (c 2.04, 95% EtOH) ; lit.[9] $[\alpha]_D$ -14.5 (c 10.0, 95% EtOH)
$C_{11}H_{18}O$, HRMS, calc. mass : 166.1358, found : 166.1358
$C_{11}H_{18}O$ calc. % : C 79.47 , H 10.91 , found : C 79.79 , H 10.91
^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.71 (3H, s, CH_3); 0.83 (3H, s, CH_3); 0.92 (3H, s, CH_3); 1.04 (3H, s, CH_3); 1.35-1.43 (2H, m, C(5) and C(6) endo H's); 1.57-1.75 (2H, m, C(5) and C(6) exo H's); 1.87 (1H, d, J=18 Hz, C(3) endo H); 2.08 (1H, dd, J=18, 3 Hz, C(3) exo H).
IR ($CHCl_3$) : ν_{max} 1734 cm^{-1} .
MS m/e(%) : 166 (M^+, 30); 122 (44); 109 (90); 82 (100); 55 (33).

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19 This term is used since we consider that 4-methylisoborneol (**5**) produced by the synthetic route outlined in Scheme 3 is enantiopure within the limits of the analytical methods described in the text. A small, finite amount (~ 0.4% ?) of **ent-5** is almost certainly present in our sample since recent investigations[20] have shown that (+)-camphor (**1**) has an enantiomeric purity of ~99.6%.
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